REMARKS

Status of the Claims.

Claims 1-18, 38, 39, 47, 49-51, and 54-67 are pending with entry of this amendment, no claims being cancelled and new claims 63-67 being added herein. The Office Action mailed on 05/24/2004 incorrectly showed claim 47 as not pending. In this regard, it is noted that Group I (claims 1-18) and Group III (claims 38-39, 47-62) were reunited in the Office Action mailed on 10/01/1998. Claims 19-37, and 40-46, 48, and 52-53 were canceled by Applicants. In addition, claim 49 (currently pending) clearly depends from claim 47. Accordingly Applicants believe claim 47 is presently pending.

Claims 38 and 47 are amended and new claims 63-67 are added herein. These amendments introduce no new matter. Support is replete throughout the specification (*e.g.*, page 6, lines 1-3, page 53, lines 5-13, page 20, lines 18-24, page 13 lines 5-29, and the like).

Information disclosure statement.

Applicants include herewith a Supplemental Information Disclosure Statement (IDS) (PTO Form 1449) containing references that have come to the attention of the inventors. Applicants request that the references cited therein be considered and made of record in the present application. To facilitate consideration of the additional references submitted herewith, Applicants have also filed a Request for Continued Examination (RCE).

Previous Office Action.

Throughout the present Office Action (mailed May 24, 2004) the Examiner refers to ". . . the reasons previously set forth in the Office Action mailed October 15, 2003. . . ". Applicants have no record of an Office Action mailed October 15, 2003. Rather the previous amendment was filed on October 15, 2004.

It appears that the Examiner is referencing the Office Action mailed on April 15, 2003 and the present response is drafted in accordance with this understanding.

35 U.S.C. §112, First Paragraph.

Office Action Paragraph 4: Claims 1-18.

The rejection of claims 1-18 under 35 U.S.C. §112, first paragraph, was maintained. In particular, the Examiner alleges that "'[g]iven the teachings of the specification and the art of record, it could not be predicted , with a reasonable expectation of success, that the invention would function as claimed' and thus one would be forced into undue experimentation to practice the claimed invention. (Office Action pages 2-3). Applicants traverse.

The prevailing scientific literature clearly establishes that YKL-40 level is a strong prognostic indicator for cancer. Thus, for example, Jensen *et al.* (2003) *Clin. Cancer Res.*, 9: 4423-4434 (see accompanying IDS), when describing earlier research, states:

> The gene for YKL-40 has been sequenced (27), and a search of the YKL-40 protein sequence against the dbest database at the National Center for Biotechnology Information using the BLAST program has shown that **YKL-40 is expressed by several types of cancer, such as colon, breast, ovarian, uterine, prostate, kidney, lung, oligodendroglioma, glioblastoma, and germ cell tumors.** Gene expression microarray analyses have shown that **the most differentially expressed gene in papillary thyroid carcinoma, glioblastoma multiforme, and extracellular myxoid chondrosarcoma was *YKL-40*** (28–30). **Serum YKL-40 levels in patients with glioma were related to tumor grade and burden (29).** We have reported previously that **increased serum levels of YKL-40 are related to poor survival in patients with metastatic breast cancer (31) and colorectal cancer (32, 33). In patients with colorectal cancer, multivariate analysis showed that elevated serum CEA and YKL-40 independently predicted short survival both preoperative and at 6-months postoperative (32, 33)**. In the present study, we evaluated the influence of serum HER2 and YKL-40 and ER status on outcome in patients with their first diagnosis of recurrent breast cancer and a possible interplay on metastatic pattern, disease-free, and overall survival. [emphasis added] (Jensen *et al.* at page 4424)

This same reference, describing the current study states:

> These findings led us to explore another growth factor, YKL-40, expressed by several types of adenocarcinomas, including breast cancer, and to compare the prognostic value of the serum levels of this protein with serum HER2 levels in patients with their first recurrence of breast cancer. **We found that high serum levels of HER2 and YKL-40 in these patients independently reflected increased aggressiveness and decreased response to**

anthracycline-based therapy. Patients with high serum levels of HER2 or YKL-40 progressed and died twice as fast as patients with normal serum levels. They were significantly sicker at recurrence and had more extensive disease with more different metastatic sites and frequent liver involvement. In a multivariate Cox analysis, **high serum levels of HER2 or YKL-40 or lack of steroid receptors at diagnosis independently doubled the relative risk of progression and dying.** This influence was maintained even after accounting for other independent prognostic variables, such as axillary nodal involvement at primary breast cancer diagnosis, lack of steroid receptors, liver metastases, more than two metastatic sites, symptomatic disease at recurrence, and the failure to induce a CR. [emphasis added] (page 4430, col. 2)

* * *

Serum HER2 and YKL-40 and absence of ERs at diagnosis exerted a comparable and mutually independent biological response modification on breast cancer aggressiveness as reflected by metastatic pattern, responsiveness to anthracycline therapy, progression, and fatal outcome. **Interestingly, high serum HER2 and high serum YKL-40 independently identified subgroups of patients with metastatic breast cancer with a poor prognosis**. [emphasis added] (page 4432, col. 1)

A study of YKL-40 as a prognostic in primary breast cancer (Johansen *et al.* (2003) *Breast Cancer Res. and Treatment*, 80: 15-21, see accompanying IDS) states:

Serum YKL-40 levels in relation to relapse-free survival and overall survival. The median followup period was 5.9 years. During this period there was a total of 77 (28%) relapses and 69 (25%) patients died. **High serum levels of YKL-40 (i.e., >age corrected 95 percentile of healthy females) at time of operation predicted shorter recurrence-free interval as compared with patients with normal serum YKL-40 (hazard ratio (HR)=1.77, 95% confidence interval (CI): 1.06–2.95, p=0.028).** The Kaplan–Meier plot is shown in Figure 1(a). Furthermore, **a significant relation was found between high serum levels of YKL-40 at time of breast cancer operation and short overall survival** (HR=1.78, 95% CI: 1.04–3.05, p =0.036). [emphasis added] (page 19, col. 1)

* * *

Interestingly the present study showed that high preoperative serum YKL-40 levels in patients with primary breast cancer reflected increased breast cancer aggressiveness since patients with high serum YKL-40 had shorter relapse-free survival and overall survival than patients with

> **normal serum YKL-40**. Furthermore multivariate Cox analysis including the classical parameters with known prognostic value in breast cancer patients showed that the serum YKL-40 level did give additional information of relapse-free survival. Serum YKL-40 is statistically significant at the 5% level for the primary endpoint (recurrence free survival) as well as the secondary endpoint (overall survival). [emphasis added] (page 19, col. 2)

This reference thus establishes that YKL-40 was a significant prognostic for both the primary endpoint (recurrence-free survival) as wella s the secondary endpoint (overall survival) in the study. Johansen *et al.* (2003) continue to state:

> The results of the present study are in accordance with studies of patients with metastatic breast cancer [21, 22] and patients with colorectal cancer [23, 24]. **A high serum YKL-40 level in breast cancer patients at time of first recurrence after first line chemotherapy and radiotherapy has been shown to predict shorter time to progression and shorter survival compared to patients with normal serum YKL-40 levels at time of first recurrence** [22]. It was also shown that **the serum YKL-40 level was an independent prognostic variable of short time to progression and death in a multivariate Cox analysis including axillary nodal involvement at primary diagnosis, ER status, liver metastases, more than two metastatic sites, symptomatic disease at recurrence and serum HER2 levels** [22]. **High preoperative serum YKL-40 levels in patients with colorectal cancer is also a prognostic parameter of short relapse-free interval and short survival** and this is independent of Dukes' stage, age, tumor localization and serum CEA [23]. Recently it has also been shown in curatively operated colorectal cancer patients that **a high postoperative serum YKL-40 level during the follow-up was a strong independent predictor of short recurrence-free interval and short survival** [24]. [emphasis added] (page 19, col 2)

A study of YKL-40 as a prognostic for ovarian cancer (Dehn *et al.* (2003) *Acta Obstet Gynecol Scand* 82: 287-293, see accompanying IDS) states:

> This is the first report of plasma concentrations of YKL-40 in patients with recurrent OC. The study showed that the **OC patients with high plasma YKL-40 at the time of the first recurrence had significantly shorter survival** than the OC patients with normal or slightly elevated plasma YKL-40. Eighty-two per cent of the patients with high plasma YKL-40 had died within 18 months after the first recurrence compared with 52% of the patients with normal or slightly elevated plasma YKL-40. We also found that **YKL-**

> **40 levels measured in a plasma sample at the time of relapse was an independent prognostic marker of survival, especially in early relapse (≤6 months after first-line chemotherapy) for patients presenting with first recurrence of OC**. [emphasis added] (page 291, col. 1)

Another study of YKL-40 as a prognostic for ovarian cancer ee accompanying IDS) states:

> Finally, analysis of the disease-free survival of stage I and II patients was evaluated in this study based on the degree of elevation of YKL-40. **Patients with an elevation of serum YKL-40 more than 80 ng/mL were significantly more likely to have recurrence of disease ($P \leq .034$) compared with patients with values less than 80 ng/mL.** Furthermore, 64% of patients with YKL-40 values more than 80 ng/mL died of disease, while none of the patients with lower preoperative YKL-40 values died. Of note, preoperative levels of CA125 and CA15-3 in these patients did not correlate with a poor outcome (data not shown). **Thus, YKL-40 can identify early-stage patients who are at high risk for recurrence and disease-related death. This could well influence treatment decisions.** [emphasis added] (DuPont *et al.* page 3338, col 1-2)

Applicants further note for the record that the concerns raised by the Examiner with regards to the standards espoused by Tockman *et al.* (1993) *Cancer Res. (Suppl)* 52: 2711-2718 (pertaining to marker selection, marker validation against endpoints, the use of specimen banks to validate the marker, confirmation of marker predictive value, *etc.*) have been met by the foregoing studies.

Moreover, the standards espoused by Tockman *et al.* pertain to the standards required for **clinical use** of a diagnostic/prognostic marker. These are the standards required for FDA approval of an assay. It is accepted law, that the standard for FDA approval goes far beyond the standard of proof required for patentability.

The prevailing scientific literature clearly indicates that YKL-40 level is an effective prognostic marker for a variety of cancers. Accordingly, no undue experimentation is required to practice the claimed invention and the rejection of claims 1-18 on these grounds should be withdrawn.

Office Action Paragraph 5: Claims 47, 49-51, and 54-62.

The rejection of claims 47, 49-51, and 54-62 under 35 U.S.C. §112, first paragraph, was maintained. The Examiner alleged that ". . . given that YKL-40 is elevated in the serum of patients with rheumatoid arthritis and liver disease, community-acquired pneumonia, inflammation of the arterial wall, bacterial meningitis, osteoarthritis, fibrosis, cirrhosis of the liver, n the absence of any nexus, it is not possible to determine or to predict whether the elevated YKL-40 found in the arthritis patients with inactive rheumatoid arthritis or the healthy woman patient were in any way associated with cancer." (see Office Action, page 5). Applicants traverse.

Like any other diagnostic or prognostic marker (*e.g.*, PSA and the like), it is intended that YKL-40 be evaluated in the context of a differential diagnosis. To clarify this, claim 47 is amended herein to recite:

> 47. **In a differential diagnosis a method of screening for an indicator for the presence of cancer**, in a mammal, said method comprising:
>
> (a) obtaining a biological sample comprising YKL-40 from said mammal; and
>
> (b) measuring the level of YKL-40 in said sample and comparing the level to the YKL-40 level found in the same samples from ~~a~~ normal healthy mammals, **wherein a statistically significant difference in YKL-40 level in the sample being tested compared to the sample from a normal healthy mammals is an indicator of the presence of a cancer** selected from the group consisting of a lung cancer, a bronchus cancer, a prostate cancer, a pancreas cancer, a stomach cancer, an ovarian cancer, a urinary bladder cancer, a brain or central nervous system cancer, a peripheral nervous system cancer, an esophageal cancer, a cervical cancer, a melanoma, a uterine or endometrial cancer, a cancer of the oral cavity or pharynx, a liver cancer, a kidney cancer, a biliary tract cancer, a small bowel or appendix cancer, a salivary gland cancer, a thyroid gland cancer, an adrenal gland cancer, an osteosarcoma, a chondrosarcoma, a liposarcoma, a testes cancer, and a malignant fibrous histiocytoma.

The specification expressly teaches the use of YKL-40 as a diagnostic marker in a differential diagnosis. Indeed, at page 13, lines 5-29, the specification expressly states:

> In diagnostic (screening) applications, a significantly elevated blood, or blood product, level of YKL-40 typically indicates one or more of four possible pathological states:
>
> 1) Acute bacterial infection (*e.g.*, any infection in which

leukocytes are known to be involved)
2) Active rheumatoid arthritis;
3) Fibrosis and cirrhosis of the liver; and
4) Cancer.

The various pathologies are easily distinguished in a differential diagnosis. For example, **an acute bacterial infection is easily characterized (*e.g.* by fever, elevated white cell count, clinical symptoms, and other criteria routinely used for the diagnosis of conditions such as Pneumonia or meningitis). Active rheumatoid arthritis is typically accompanied by joint pain, swollen and tender joints, and by the elevated acute phase reactants, C-reactive protein and erythrocyte sedimentation rate**.

A possible diagnosis of fibrosis or cirrhosis of the liver can be confirmed or eliminated by a liver biopsy and by serum levels of liver enzymes and albumin.

Having eliminated bacterial infection, active rheumatoid arthritis, and cirrhosis, the remaining candidate is a cancer. At this point the patient is a good candidate for follow-up cancer detection/diagnostic strategies that are well known to those of skill in the art. These include, but are not limited to CAT scans, X rays, mammography, bone scintigraphy, PET scans, assaying of other molecular markers for cancer(s) (*e.g.*, PSA, *etc.*), and the like.

Thus, in general, any diagnosis indicated by YKL-40 measurements made according to the methods of the invention will be independently confirmed with reference to clinical manifestations of disease known to practitioners of ordinary skill in the clinical arts. [emphasis added]

It is well established that YKL-40 levels are not elevated in healthy subjects. With respect to the various pathologies associated with elevated YKL-40, as indicated above, any clinician can routinely distinguish between the various conditions (rheumatoid arthiritis, meningitis, cancer, *etc.*). Thus, no undue experimentation is required to screen for YKL-40 level in a differential diagnosis, as recited in claim 47.

Moreover, contrary to the Examiner's assertion practice of the claimed method does not require that one of skill distinguish between the various recited cancers. In making this assertion, the Examiner reads a limitation into the claims that is not present.

Rather, as written, the claims indicate that, in the context of a differential diagnosis, elevated YKL-40 can be a marker for a cancer listed in the recited Markush group. As indicated in the specification, elucidation of the particular type of cancer can be accomplished using "follow-up cancer detection/diagnostic strategies. . ." such as ". . . CAT scans, X rays, mammography, bone scintigraphy,

PET scans, assaying of other molecular markers for cancer(s) (e.g., PSA, etc.), and the like". The claim merely recites screening for a particular indicator (*e.g.,* YKL-40) which can then lead the clinician to appropriate follow-up tests.

Accordingly, no undue experimentation is required to practice the methods recited in claims 47, 49-51, and 54-62, and the rejection on these grounds should be withdrawn.

Office Action Paragraph 6: Claims 38-39.

The rejection of claims 38-39 under 35 U.S.C. §112, first paragraph, was maintained. The Examiner stated that the specification ". . . while enabling for a method to screen for a cancer comprising measuring the levels of YKL-40 in a fluid sample from a cancer patient, wherein the YKL-40 level is greater than the 95th percentile for normal controls, does not reasonably provide enablement of said method wherein a statistically significant difference in YKL-40 level compared to the sample from a normal healthy mammal indicate the presence of a cancer." Applicants traverse.

While Applicants disagree with the Examiner's position, to expedite prosecution, claim

> 38. A method to screen for recurrence of a cancer after removal of a primary tumor, said method comprising:
>
> (a) obtaining a biological sample comprising YKL-40 from a cancer patient following removal of a primary tumor selected from the group consisting of a lung cancer, a bronchus cancer, a colorectal cancer, a prostate cancer, a pancreas cancer, a stomach cancer, an ovarian cancer, a urinary bladder cancer, a brain or central nervous system cancer, a peripheral nervous system cancer, an esophageal cancer, a cervical cancer, a melanoma, a uterine or endometrial cancer, a cancer of the oral cavity or pharynx, a liver cancer, a kidney cancer, a biliary tract cancer, a small bowel or appendix cancer, a salivary gland cancer, a thyroid gland cancer, an adrenal gland cancer, an osteosarcoma, a chondrosarcoma, a liposarcoma, a testes cancer, and a malignant fibrous histiocytoma; and
>
> (b) measuring a level of YKL-40 in said sample and comparing the sample YKL-40 level to the YKL-40 level found in **normal controls** wherein a sample YKL-40 level in **statistically significant excess of YKL-40 levels in normal controls** is an indicator of a possible recurrence of said cancer.

This language is in accordance with that indicated by the Examiner as enabled. While a particular confidence level is not recited in the claim, Applicants believe no such recitation is required one of ordinary skill in the art readily understands the meaning of a statistically significant difference (*i.e.,* confidence level). In support of this one the Examiner's attention is directed to any of the papers

accompanying the present response in which statistically significant YKL-40 levels are routinely identified.

Accordingly, the rejection of claims 38-39 under 35 U.S.C. §112, first paragraph, on these grounds should be withdrawn.

Office Action Paragraph 7: Claims 1-18, 38-39, 49-51, and 54-62.

The rejection of claims 1-18, 38-39, 49-51, and 54-62 under 35 U.S.C. §112, first paragraph, was maintained. In particular, the Examiner alleged that the specification, while being enabling for claimed methods in carcinoma cancers, does to reasonable provide enablement of said methods in the plethora of cancers claimed in claims 1, 38, and 47. Applicants traverse.

As noted in the references cited above:

1) YKL-40 is expressed by several types of cancer, such as **colon**, **breast**, **ovarian**, **uterine**, **prostate**, **kidney**, **lung**, **oligodendroglioma**, **glioblastoma**, and **germ cell tumors**. (*see Jensen et al.* (2003), *supra*)

2) Gene expression microarray analyses have shown that the most differentially expressed gene in papillary **thyroid carcinoma**, **glioblastoma multiforme**, and **extracellular myxoid chondrosarcoma** was YKL-40 (28–30). (*see Jensen et al.* (2003), *supra*)

3) Serum YKL-40 levels in patients with **glioma** were related to tumor grade and burden (29). (*see Jensen et al.* (2003), *supra*)

4. Increased serum levels of YKL-40 are related to poor survival in patients with **metastatic breast cancer** (31) and **colorectal cancer** (32, 33). (*see Jensen et al.* (2003), *supra*)

5. The study showed that the OC [**ovarian cancer**] patients with high plasma YKL-40 at the time of the first recurrence had significantly shorter survival. (*see, e.g.,* Dehn *et al.* (2003) *supra*).

6. [T]he present study showed that high preoperative serum YKL-40 levels in patients with **primary breast cancer.** (*see, e.g.,* Johansen *et al.*(2003) *supra*).

YKL-40 expression is thus clearly implicated or demonstrated as an effective marker for:

1) colon cancer
2) breast cancer
3) ovarian cancer
4) uterine cancer
5) prostate cancer
6) kidney cancer
7) lung cancer
8) oligodendroglioma
9) papillary thyroid carcinoma
10) glioblastoma,
11) germ cell tumors
12) papillary thyroid carcinoma
13) glioblastoma multiforme
14) extracellular myxoid chondrosarcoma
15) glioma
16) metastatic breast cancer
17) colorectal cancer
12) glioblastoma multiforme

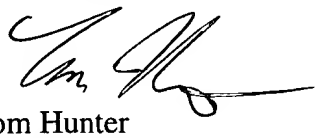
in a number of different studies.

In view of the overwhelming evidence of implicating YKL-40 expression in a large number of cancers, Applicants believe the specification is fully enabling for the cancers recited in the presently pending claims. Accordingly the rejection of claims 1-18, 38-39, 49-51, and 54-62 under 35 U.S.C. §112, first paragraph, on these grounds should be withdrawn.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. **Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor**. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

QUINE INTELLECTUAL PROPERTY LAW
GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,



Tom Hunter
Reg. No: 38,498